REMARKS

Applicants respectfully request reconsideration and allowance of the present application.

CLAIMS STATUS

Claims 15-17 and 19-25 are pending.

Claims Rejections – 35 U.S.C. § 103

Claims 15-17, 19-21, 23, and 25 stand rejected as obvious over WO 01/32158 ("Piper") in view of *Practical Pharm. Prep. Tech.*, January 1999, pp. 203-04 ("Zhuang"), as evidenced by *Remington: The Science and Practice of Pharmacy,* 21st Edition, 2003, pp. 675-676 ("Remington") and RxList: the Internet Drug List (http://www.rxlist.com/actos-drug.htm). Applicants respectfully traverse.

The PTO failed to establish a *prima facie* case of obviousness at least for the following reasons:

1) the PTO failed to make its obviousness analysis explicit at least because it relies on a factually inaccurate assumption that glyburide and pioglitazone are totally interchangeable;

2) the PTO ignores the unexpected results presented in Masahiko Koike's declarations of March 12, 2010 and July 24, 2009;

3) Piper relates to a low dose pharmaceutical formulation, while the object of the present invention is to use pioglitazone hydrochloride and metformin hydrochloride in the same doses as the approved doses thereof.

1) the PTO failed to make its obviousness analysis explicit.

Prior to addressing the rejection, Applicants bring the PTO's attention to the legal standard for obviousness rejections from the Supreme Court decision *KSR Int'l Co. v. Teleflex, Inc., 550 U.S. 398 (2007)*, which MPEP § 2141 summarizes as follows:

> "The key to supporting any rejection under 35 U.S.C. 103 is the clear articulation of the reason(s) why the claimed invention would have been obvious. The Supreme Court in *KSR* noted that the analysis supporting a rejection under 35 U.S.C. 103 should be made explicit. The Court quoting *In re Kahn,* 441 F.3d 977, 988, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006), stated that "'[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness.'" *KSR*, 550 U.S. at ___, 82 USPQ2d at 1396."

Applicants respectfully submit that the rejection is largely based on the PTO's assumption that glyburide and pioglitazone are totally interchangeable. See e.g. Office Action, page 4, last paragraph, where the PTO asserts that pioglitazone is a functional equivalent of glyburide. See also, Office Action, page 9, second full paragraph, where the PTO asserts that one of ordinary skill in the art would be motivated to use the same size for pioglitazone particles as for glyburide particles.

Although both glyburide and pioglitazone can be broadly classified as antidiabetic drugs, contrary to the PTO's assumptions and assertions, they are not totally interchangeable; they are not functional equivalents and one of ordinary skill in the art would not be motivated to use a physical parameter, such as a particle size, disclosed for one of them in making a formulation or preparation for the other. Applicants enclose with the present response the labels of Diaßeta® (glyburide) and ACTOS® (pioglitazone hydrochloride) to emphasize the following drastic differences between glyburide and pioglitazone:

1) Chemical structures of glyburide and pioglitazone are completely different.

2) The doses are different. The dose of pioglitazone hydrochloride is 15, 30 or 45 mg, whereas the dose of glyburide is 1.25, 2.5 or 5 mg.

3) Glyburide is an acidic compound, whereas pioglitazone hydrochloride is a basic compound.

4) Glyburide has an insulin secretagogue action, whereas pioglitazone hydrochloride does not.

5) Glyburide does not have an insulin sensitizing action, whereas pioglitazone hydrochloride does.

6) Glyburide mainly acts on pancreas alone, whereas pioglitazone hydrochloride mainly acts on adipose tissue, muscle and liver.

7) Glyburide potentially causes hypoglycemia, whereas pioglitazone hydrochloride does not.

8) Glyburide exhausts pancreas, whereas pioglitazone hydrochloride does not.

9) Glyburide and pioglitazone show different dissolution property influential on drug efficacy (pioglitazone does not dissolve in the neutral pH, whereas glyburide does) and different biomembrane permeability (glyburide shows higher permeability).

Applicants provide additional details regarding the differences between glyburide and pioglitazone below. Pioglitazone hydrochloride shows the highest solubility at pH 1.1 (6700 μg/mL), markedly lower solubility as the pH increases, and scarce dissolution near neutral pH (pH 2.0: 420 μg/mL, pH 3.0: 14 μg/mL, pH 5.0: 0.26 μg/mL, pH 7.0: 0.093 μg/mL). In contrast, glyburide scarcely dissolves in the acidic range, shows increased solubility as the pH increases, and high solubility near neutral pH (pH 7.4: 13 μg/mL), for details see the enclosed European Journal of Pharmaceutical Science 29 (2006) 45-52, Fig. 1 and Interview Form of Actos, P.4, 2nd Table.

In sum, based on the references cited by the PTO, one of ordinary skill in the art would not have arrived at the particles of pioglitazone or a salt thereof have a median size of 2-10 μm recited in the pending claims. Accordingly, because the PTO failed to establish a *prima facie* case of obviousness, Applicants request withdrawal of the rejection.

2) The PTO ignores the unexpected/surprising results presented in Masahiko Koike's declarations of March 12, 2010 and July 24, 2009. In particular, the PTO asserts that "unexpected bioequivalence of pioglitazone would be an obvious expected result of the suggested formulation of Piper," see Office Action, page 9.

In response to this assertion, Applicants respectfully submit that Piper does not achieve bioequivalence (BE), and one of ordinary skill in the art would not have expected in vivo interaction of metformin with the other antidiabetic agents that can be combined with metformin based on Piper's teaching at the time the present invention was made.

As Applicants explained above, glyburide and pioglitazone have drastically different solubility properties. To repeat, pioglitazone hydrochloride shows the highest solubility at pH 1.1 (6700 μg/mL), markedly lower solubility as the pH increases, and scarce dissolution near neutral pH (pH 2.0: 420 μg/mL, pH 3.0: 14 μg/mL, pH 5.0: 0.26 μg/mL, pH7.0: 0.093 μg/mL), while in contrast to pioglitazone, glyburide scarcely dissolves in the acidic range, shows increased solubility as the pH increases, and high solubility near neutral pH (pH 7.4: 13 μg/mL).

Metformin hydrochloride is a compound with pKa 12.4, which alkali shifts the environment upon dissolution. Therefore, the delayed dissolution in the stomach by the addition of metformin hydrochloride is specific to pioglitazone hydrochloride and is not and cannot be found with glyburide.

To achieve bioequivalence (BE), it is a general practice for those of ordinary skill in the art to use a drug formulation having a particle size as that for an approved commercial product. Following such general practice, a preparation with 13 μm pioglitazone particles, which a median size for commercially approved pioglitazone hydrochloride, was used in the initial bioequivalence experiments in humans. Because the increase in the gastric pH due to metformin hydrochloride is too small, the result of non-bioequivalence was observed in these initial experiments. However, when a size of pioglitazone particles was reduced to 2-10 μm, it was surprisingly found that bioequivalence of pioglitazone is achieved. Applicants respectfully submit that one of ordinary skill in the art could not have predicted the bioequivalence for pioglitazone particles having a median size of 2-10 μm as the pending claims recite.

In sum, in view of the surprising results presented Masahiko Koike's declarations of March 12, 2010 and July 24, 2009 as well as in the second supplemental declaration enclosed with present response, Applicants respectfully request withdrawal of the rejection.

3) Piper relates to a low dose pharmaceutical formulation, while the object of the present invention is to use pioglitazone hydrochloride and metformin hydrochloride in the same doses as the approved doses thereof.

Piper discloses a low dose pharmaceutical formulation comprising metformin and another antidiabetic agent, wherein use of glyburide as the other antidiabetic agent is preferred. Piper describes that the combination provides at least substantially equivalent efficacy in treating diabetes in drug naïve patients (in first line therapy) as do combinations of substantially higher dosages as prescribed in generally accepted medical practice for the first-line therapy in treating diabetes (P.6, line 28 - P.7, line 1, claim 1 etc.).

In the present invention, pioglitazone hydrochloride and metformin hydrochloride are used in the same doses as the approved doses thereof as single drugs (pioglitazone hydrochloride: 15 mg, metformin hydrochloride: 500 mg or 850 mg), and reduction of the dose is not intended. The present invention aims to provide a compact tablet easily handled by patients, which is as safe as the single drugs since it shows BE to the approved single drugs. The combination drug of the present invention containing pioglitazone hydrochloride and metformin hydrochloride in the same doses as the single drugs is already on the US, Europe and Japan markets.

For the record, Applicants submit that Zhuang does not apply to the present invention.

As shown in Table DD4 of the enclosed second supplemental Declaration by Masahiko Koike, the particle size of metformin hydrochloride is 29 μm, that of pioglitazone hydrochloride in a non-micronized lot is 18.5 μm (mixture with microcrystalline cellulose; 13 μm for pioglitazone hydrochloride alone), and 7 μm for micronized lot. The median size ratio is far from 1:1, and therefore, the cited reference Zhuang does not apply thereto.

Claims 22 and 24 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over Piper in view of Zhuang, as evidenced by Remington and RxList and US 6,117,451 ("Kumar"). Applicants respectfully traverse.

Claims 22 and 24 are non-obvious because Kumar does not remedy the discussed above deficiencies of Piper and Zhuang.

On an additional note, the PTO failed to establish a *prima facie* case of obviousness because the PTO relies on factually inaccurate assertions in its obviousness analysis. For example, on page 7, 3rd paragraph, the PTO asserts as follows: "As suggested by Kumar, it is known in the art to optimize and manipulate tablet hardness depending on a tablet's excipients and desired dissolution rate."

Applicants respectfully submit that the above cited assertion is factually inaccurate.

As shown in the following Tables, the tablet of the present invention shows rapid dissolution over a wide hardness range, which confirms that contrary to the PTO's assertion, the dissolution property does not depend on the hardness.

Pioglitazone HCl 15 mg / Metformin HCl 500 mg

Hardness (N)	126	170	232
dissolution rate after 30 min (%)			
Pioglitazone	102	103	102
Metformin	101	101	102

Pioglitazone HCl 15 mg / Metformin HCl 850 mg

Hardness (N)	178	218	297
dissolution rate after 30 min (%)			
Pioglitazone	102	102	101
Metformin	99	100	99

In sum, at least for the reasons discussed in this section, Applicants request withdrawal of the rejection.

CONCLUSION

Applicants believe that the present application is in condition for allowance and thus respectfully request favorable reconsideration of the application. The Office is invited to contact the undersigned by telephone if a telephone interview would advance the prosecution of the present application.

The Office is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, the Applicants hereby petition for such extension under 37 C.F.R. § 1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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By Alexey V. Saprigin
Reg #56,439
for Stephen B. Maebius
Attorney for the Applicants
Registration No. 35,264

FOLEY & LARDNER LLP
Customer Number: 22428
Telephone: (202) 672-5569
Facsimile: (202) 672-5399